Research Report

Correlation of Inhibin A Serum Level with Preeclampsia

Hubungan antara Kadar Inhibin A Serum dengan Preeklampsia

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Abstract

Objective: The purpose of this research is to analyze the difference of Inhibin A serum level between preeclampsia patients with normal pregnant patients and to analyze the relation between Inhibin A serum level with preeclampsia.

Method: Comparison of average Inhibin A serum level of the preeclampsia group with normal pregnancy was analyzed by using Mann-Whitney test, and the correlation between Inhibin A serum level and preeclampsia was using biserial point correlation test. Samples were obtained from blood of patient suffered preeclampsia and also normal pregnancy, each containing 17 samples according inclusion and exclusion criterias. Patients came to Hasan Sadikin Hospital and two satellite hospitals in August to November 2010.

Result: Characteristic test in two groups of study showed that both groups were homogeny and could compared. Mean level of Inhibin A serum was higher in preeclampsia (1268.08 pg/ml) than normal pregnancy (911.12 pg/ml) (p = 0.042) there was a strong positive correlation between Inhibin A serum level with preeclampsia (r pbi = 0.354; p = 0.027).

Conclusion: From this research, we can conclude that Inhibin A serum level in preeclampsia is higher than normal. There is a positive correlation of Inhibin A serum level with preeclampsia.

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Keywords: inhibin A serum, normal pregnancy, preeclampsia

Abstrak

***Tujuan**: Tujuan penelitian ini adalah menganalisis perbedaan kadar Inhibin A serum pada penderita preeklampsia dengan kehamilan normal dan menganalisis hubungan antara kadar Inhibin A serum dengan preeklampsia.*

***Metode**: Perbandingan rerata kadar Inhibin A serum kelompok preeklampsia dengan kehamilan normal menggunakan uji Mann-Whitney, dan korelasi antara kadar Inhibin A serum dengan preeklampsia menggunakan uji korelasi point biserial. Sampel diperoleh dari darah pasien preeklampsia dan kehamilan normal dengan masing-masing sebesar 17 sampel sesuai dengan kriteria inklusi dan eksklusi. Subjek penelitian datang ke RS Dr. Hasan Sadikin Bandung dan dua rumah sakit jejaring periode Agustus sampai November 2010.*

***Hasil**: Uji karakteristik pada kedua kelompok penelitian menunjukkan kedua kelompok homogen dan dapat diperbandingkan. Rerata kadar Inhibin A serum pada preeklampsia lebih tinggi (1268,08 pg/ml) dibandingkan dengan kehamilan normal (911,12 pg/ml) (p = 0,042). Terdapat korelasi positif antara kadar Inhibin A serum dengan preeklampsia (r pbi = 0,354; p = 0,027).*

***Kesimpulan**: Pada penelitian ini dapat disimpulkan bahwa kadar Inhibin A serum pada preeklampsia lebih tinggi dari kehamilan normal. Terdapat hubungan positif antara kadar Inhibin A serum dengan preeklampsia*

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***Kata kunci**: inhibin A serum, kehamilan normal, preeklampsia*

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INTRODUCTION

Preeclampsia is a pregnancy complication syndrome marked by blood pressure increment and proteinurine in a pregnant woman that never has any history of hypertension. Usualy this syndrome appears in late 2nd trimester to early 3rd trimester of pregnancy and diminishes or disappears after birth.[1,2]

Preeclampsia incidence in multiparity varies but still lower than nulliparity. It is highly influenced by parity, ethnic, race, and genetical predisposition.[2] In Asia, preeclampsia incidence varies, in Burma, China, Thailand and Vietnam is around 0.4 - 4.9%, Singapore is a 0.13 - 6.66%. Indonesia's incidence Of preeclampsia approximately 3.4 - 8.5% of all pregnancy.[3] According to Padjadjaran University Faculty of Medicine Obstetrics and Gynecology department's annual reports from 2007 - 2009 in Hasan Sadikin Hospital, the incidence of mild preeclampsia is 0.97 - 2.08%, while severe preeclampsia rates to 1.33 - 2.94%.[4-6]

Eclampsia is one of preeclampsia complications that causes maternal morbidity and mortality. Maternal mortality rate due to eclampsia in USA is 1 in 2000 to 3000 pregnancies, while in developing countries is 1 in 100 to 1700 pregnancies.[7]

The preeclampsia pathophysiology theory that is believed until now is 2 phase theory of preeclampsia by placenta as the trigger. It is begun at 1st phase of failed trophoblast invasion to maternal spiral arteries which than continues to 2nd phase of clinical syndrome of hypertension and proteinurine. In a normal process of implantation, the trophoblasts invasion of maternal spiral arteries continues to a remodeling process. The trophoblastic cells replace the endothelial and muscular layer of arteries so it would dilate the arteries' diameter. In preeclampsia, abnormal shallow process of trophoblast invasion occurs, causes the more profound myometrial arteries not losing the en-

dothel and muscular layers, and therefore only few parts of arteries that dilate compare to normal dilatation.[2]

The cellular mechanism of implantation and trophoblast invasion processes are so complex that until now it is not fully understood yet. Multiple factors participate in such process e.g. growth factors, peptide hormones, steroid hormones, cytokines and immune factors. One of the growth factors is Inhibin A. Inhibin A is a dimeric glycoprotein originates from transforming growth factor ß superfamily, consists of αßA (Inhibin A) dan αßB (Inhibin B), synthesized by anterior hypophysial gland, granulose cell and other tissues as well. In early pregnancy it is produced by corpus luteum and then produced by placenta especially by cytotrophoblasts. Inhibin A is known as a FSH-releasing hormone regulator, but recent evidences demonstrate an important local action of Inhibin A especially as a paracrine regulator in reproduction function. Other growth factor include in transforming growth factor ß superfamily is Activin. It serves as a modulator of cellular proliferation and differentiation, apoptosis of tissue remodeling and in inflammation. Local function of Inhibin A is unknown yet, and the synthesis of subunit a is limited to endocrine organs.[8]

Inhibin A and Activin are expressed widely in endometrium, especially have a role in implantation preparation and decidualization of endometrial stroma. During the decidual invasion process by trophoblasts, the existence of Inhibin A, Activin and other growth hormones can be detected at 7 - 8 days of pregnancy. Activin and Inhibin A have opposite properties, Activin supports this process, while Inhibin A and macrophage inhibitory cytokine-1 (MIC-1) inhibit the process. In trophoblasts invasion failure of preeclampsia hypoxia would occur at the surface of syncitiotrophoblast. This then will provoke repair response by cytotrophoblast by stimulating the secretion of arterial growth factors of angiogenic protein such as Vascular Endotehelial growth factor (VEGF), Placental growth factor (PLGF), dan Transforming growth factor ß (TGF-ß) which consists of Inhibin A. The increment of Inhibin A serum in preeclampsia can be detected from 10 weeks of gestational age that exceeds normal pregnancy level.[9-11]

In researches conducted by experts of preeclampsia, controversial results are still the issue regarding the Inhibin A serum in relation to trophoblast invasion disturbance as etiology of preeclampsia. Phupong[12], Muttukhrisna[13], and Palwattananupant[14] explain in their research that there is appositive relation of Inhibin A serum level with trophoblast invasion disturbance in preeclampsia. In other research conducted by Raty[15] and Emma[16] no relation was found. So, from the previous explanation, to add justification of the preliminary research, researcher feels the necessity to conduct a research to prove the difference among those results. This research is purposed to analyze the difference between Inhibin A serum level in preeclampsia compared to normal pregnancy and to analyze the relation between Inhibin A serum level with preeclampsia. The measurement technique of Inhibin A in this research is done by ELISA.

METHOD

The method used in this research is cross sectional study with correlation analysis. Comparison of mean concentrations of serum Inhibin A between group of pre-eclampsia with normal pregnancies using the Mann-Whitney test, and correlation between Inhibin A serum levels with severity of preeclampsia using biserial point correlation test. Selection of study subjects were determined by consecutive sampling.

RESULTS

This research was conducted from August 2010 until November 2010. During that period it was obtained 34 research subjects who fulfilled the inclusion criterias, which consisted of 17 subjects aged ≥ 28 weeks pregnant women with preeclampsia and 17 normal pregnant subjects aged ≥ 28 weeks as the control group. Study subjects were from patients who come to the outpatient clinic of Obstetrics and Gynecologic RS Dr. Hasan Sadikin, RS dr. Slamet Garut, and RSUD Sumedang. Both groups were performed a blood sampling to check levels of Inhibin A in the Prodia Laboratory Jakarta.

All study subjects were assessed for baseline examination that included age, parity, and gestational age. Results shown in the tables below.

Table 1. Subject Characteristics.

Characteristics	Research Group		Total	Statistic Test
	Preeclampsia (n=17)	Normal (n=17)		
Age (year)				
< 25	2	6	8	t = 1.991
25 - 34	10	8	18	p = 0.055
> 35	5	3	8	
Mean (± SD)	31.5 (5.7)	27.1 (7.1)		
Range	20 - 40	16 - 43		
Parity				
0	8	8		χ^2 = 0.0
1 - 3	9	9		p = 1.0
Gestational Age (week)				
< 37	8	4		
37 - 41	9	13		Zmw = 0.332
Mean (± SD)	35.8 (4.0)	36.5 (2.9)		p = 0.760
Range	28 - 41	30 - 39		

Note: χ^2 = Chi-Square; t = t test; p = 0.05 significant

Table 1 shows that the mean age of mothers in both groups showed no significant difference (p = 0.055). In preeclampsia group, maternal age range was 20 - 40 years and in the normal pregnancy group the maternal age range is 16 - 43 years. Similarly, parity showed no significant difference (p = 1.0). The mean gestational age between the two groups have value of p = 0.760. Thus, these two groups were homogeneous so that proper studies can be compared.

Table 2. Comparison of mean Inhibin A concentration between preeclampsia and normal pregnancy groups.

Variable	Research Group		Statistic Test
	Preeclampsia (n = 17) (pg/ml)	Normal Pregnancy (n = 17) (pg/ml)	
Inhibin A Concentration:			
Mean (SD)	1268.08 (510.68)	911.12 (497.66)	t = 1.802
Median	1380.6	973.15	p = 0.042
Range	453.2 - 1900	131.3 - 1609.3	

Note: Z_{M-W} (Mann-Whitney test (p = 0.042); biserial point correlation (r pbi = 0.354; p = 0.027)

Table 2 presents comparative data on mean concentrations of Inhibin A between preeclampsia and normal pregnancy group. Using Mann-Whitney test, levels of Inhibin A in preeclampsia group was higher (1268.08 pg/ml) when compared with normal pregnancy group (911.12 pg/ml). Range Inhibin A serum levels in preeclampsia group is 453.2 to 1900 pg/ml and in normal pregnancy group is 131.3 to 1609.3 pg/ml with significant statistical value (p = 0.042). It can be concluded that serum levels of Inhibin A was higher in preeclampsia compared with normal pregnancies.

Table 2 shows that there is a significant correlation between levels of Inhibin A serum with the incidence of preeclampsia (p = 0.027) with the positive biserial point correlation (r pbi = 0.354).

Table 3. Correlation between levels of Inhibin A serum and degree of preeclampsia.

Inhibin A (pg/ml)	Preeclampsia	
	Mild (n = 4)	Severe (n = 13)
Mean (± SD)	546.2 (78.9)	1239.4 (578.5)
Median	545.6	1321.2
Range	453.2 - 636.3	57 - 1900

Note: r pbi = 0.486; p = 0.048

Table 3 shows that there is a significant correlation between levels of Inhibin A serum with a degree of preeclampsia (p = 0.048) with positive correlation (r pbi = 0.486).

DISCUSSION

Subjects Characteristics

The frequency of preeclampsia for each country vary due to many factors such as primigravida, socio-economic status, the difference criteria in determining the diagnosis, and others. In primigravida, the frequency of preeclampsia was higher compared with multigravida, especially the young primigravida. Diabetes mellitus, hydatidiform mole, multiple pregnancy, hydrops fetalis, age more than 35 years, and obesity are predisposing factors for preeclampsia.[17]

Gestational age is very influential in the clinical course of preeclampsia. Dekker and Sibai found that began early second trimester of pregnancy or gestational age more than 12 weeks, pregnant women who are destined to develop preeclampsia showed a significant decrease of T helper cells compared with women with normal blood pressure.[2] Another study conducted by Bardeguez et al found that the occurrence of an increase in the formation of antibodies on endothelial cells that are found in more than 50 percent of women was in line with the increasing age of preeclampsia.[2] On the basis of statistical analysis on the characteristics of the three variables of research subjects, the two research groups are homogeneous so that it can be compared.

Comparison of Mean Levels of Inhibin

Result from the above line are consistent with previous research that has been done by Muttukrishna et al, who studied the levels of Inhibin A in 20 women with preeclampsia and 20 women with normal pregnancies. Inhibin A levels were significantly increased in serum preeclampsia.[18] Phupong found that levels of Inhibin A is greater in the preeclampsia group than the normal pregnancy.[12] According to Rohra et al, serum levels of Inhibin A in preeclampsia was 10 times higher than in normal pregnancy.[10] Research conducted by Khalil A, et al showed that the serum levels of Inhibin A detected in normal pregnant women was 1.26 ± 0.32 pg/ml, whereas the levels found in preeclampsia was 2.69 ± 1,41 pg/ml.[19] Palwattananupant and Phupong in their research concluded that serum levels of Inhibin A in preeclampsia was greater (1229.7 ± 537.5 pg/ml) compared with normal pregnancies (839.1 ± 370.0 pg/ml).[14] Therefore, we can conclude that the result of this study support the hypothesis that there are increased serum levels of Inhibin A in preeclampsia when compared with normal pregnancy.

Relationship between Serum Levels of Inhibin A in Degree of Preeclampsia

The results above are consistent with the study conducted by Zeeman et al in 2000, that measure levels of Inhibin A from all the women who were treated at Parkland Hospital for evaluation of pregnancy induced hypertension. In that study found levels of Inhibin A was greater than 3196 pg/ml. That high levels of Inhibin A was found in the group of women with severe preeclampsia. Inhibin A levels significantly correlated with the degree of hypertension in pregnancy. Specifically, using normal pregnancies as control group, Zeeman et al concluded that the levels of Inhibin A increased significantly in severe preeclampsia.[20]

CONCLUSION

Inhibin A serum levels higher in patients with preeclampsia compared with normal pregnancies and there is a positive relationship between levels of Inhibin A serum with preeclampsia.

REFERENCES

1. Wang Y, Alexander J. Placental pathophysiology in preeclampsia. Pathophysiology. 2000; 6: 261-70
2. Cunningham F, Leveno K, Bloom S, Hauth J, Rouse D, Spong C. Williams Obstetrics. 23rd Ed. New York: Mc-Graw Hill; 2010
3. Ventura SJ, Martin JA, Curtin SC, Menaker F, Hamilton BE. Births: final data for 1999 National Vital Statistics Reports. 2001; 49(1): 49
4. Annual Report 2009. Bandung: Obstetrics and Gynecology Medical Faculty University of Padjadjaran, Hasan Sadikin Hospital Bandung; 2010
5. Annual Report 2008. Bandung: Obstetrics and Gynecology Medical Faculty University of Padjadjaran, Hasan Sadikin Hospital Bandung; 2009
6. Annual Report 2007. Bandung: Obstetrics and Gynecology Medical Faculty University of Padjadjaran, Hasan Sadikin Hospital Bandung; 2008
7. Maria J, Trace K, Rickerdy F, Christian B, Donna N, Joshua C. Characteristics of preeclampsia and eclampsia-related maternal death in rural Haiti. J Matern Fetal Neonatal Med. 2005; 18(5): 343-8
8. Jones R, Salamonsen L, Findlay J. Potential roles for endometrial inhibin, activins and follistation during human embryo implantation and early pregnancy trends in embriology and metabolism. Elsevier Science Ltd. 2002
9. Jones R, Stoikos C, Findlay J, Salamonsen L. TGF-beta superfamily expression and actions in the endometrium and placenta. Reproduction. 2006; 132(2): 217-32
10. Rohra DK, Qidwai N. Biochemical screening for the prediction of preeclampsia; J Pak Med Assoc. 2005; 55(2): 79-82
11. Reddy A, Suri S, Sargent IL, Redman CW, Muttukrisna S. Maternal circulating levels of inhibin A, activin A, sFlt-1 and endoglin at parturition in normal pregnancy and preeclampsia. PLoS One. 2009; 4(2): e4453
12. Phupong V, Paiwattananupant K, Honsawek S. Inhibin A levels and severity of preeclampsia. Arch Gynecol Obstet. 2008; 280: 183-6
13. Muttukhrisna S. Role of inhibin in normal and high risk pregnancy. Semin Reprod Med. 2004; 22: 227-34
14. Palwattananupant K, Phupong V. Serum Inhibin A level in preeclampsia and normotensive pregnancy. Hypertension Pregnancy. 2008; 27(4): 337-43
15. Räty R, Koskinen P, Alanen A, Irjala K, Matinlauri I, Ekblad U. Prediction of Preeclampsia with Maternal Mid trimester Total Inhibin A, Renin, AFP and free ß-hCG Levels. Prenat Diagn. 1999 Feb; 19(2): 122-7
16. Emma J, Simon C, Stephen A, Catherine H, Nigel P, Cameron W. Maternal serum inhibin, activin, human chorionic gonadothropin and a-fetoprotein as second trimester predictor of preeclampsia. BJOG. 2003; 110: 46-52
17. Report of national high blood pressure education program working group on high blood pressure in pregnancy. Am J Obstet Gynecol. 2000; 183(1): 1-22
18. Muttukrishna S, Knight P, Groome N, Redman C, Ledger W. Activin A and inhibin A as possible endocrine markers for pre-eclampsia. Lancet. 2007; 349: 1285-8
19. Khalil A, Kaufmann R, Wortsman J, SJ SW, Huffman D. Inhibin in normal and abnormal pregnancy: maternal serum concentration and partial characterization. Am J Obstet Gynecol. 1995; 172(3): 1019-25
20. Zeeman G, Alexander J, McIntire D, Byrd W, Leveno K. Inhibin-A levels and severity of hypertensive disorders due to pregnancy. Obstet Gynecol. 2002; 100(1): 140-4